CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLORMEQUAT CHLORIDE

Chemical Code # 001512, Tolerance # 50508
SB 950 # 256

Original date: 12/24/02

I. DATA GAP STATUS

Combined, Rat (chronic/onco):	Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated.
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated.
Teratology, rat:	No data gap, acceptable study, no adverse effect.
Teratology, rabbit:	No data gap, acceptable study, no adverse effect.
Gene mutation:	No data gap, acceptable study, no adverse effect
Chromosome effects:	No data gap, acceptable study, no adverse effect.
DNA damage:	Data gap, unacceptable study, no adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 117574 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T021224
Original: Kishiyama & Silva, 12/24/02

Chlormequat chloride is registered in California as a plant growth regulator for ornamentals. There are three products currently registered. This chemical has been grouped by US EPA with other aliphatic alkyl quaternaries as one case. The lead for this group at DPR is didecyl dimethyl ammonium chloride (CC 1682), which has a complete data base with no adverse effects identified.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

50508 - 002 037680 "Two-Year Rat Feeding Experiment with Chlor-Choline-Chloride," (BASF Institute for Industrial Hygiene & Pharmacology, 12/9/66). Chlor-Choline-Chloride (purity not stated) was fed in diet to BASF bred Sprague-Dawley rats (50/sex/dose) at 0 (cellulose), 500 and 1000 ppm for two years. No treatment related effects reported. UNACCEPTABLE. Not upgradeable (No MTD; too few dose levels, numerous other deficiencies. The study was conducted prior to FIFRA Guidelines. No adverse effect. (Kishiyama & Silva, 12/5/02).

CHRONIC TOXICITY, RAT

See combined, Rat

CHRONIC TOXICITY, DOG

50508 - 002 037682, "Two-Year Dog Feeding Experiment with Chlor-Choline-Chloride", (BASF Institute for Industrial Hygiene & Pharmacology, Switzerland, 4/17/67). Chlorocholine, purity not stated, was fed in diet to Beagle dogs (3/sex/dose) at 100, 300, or 1000 ppm for two years. An additional treatment group at 1000 ppm chlorocholine chloride + 700 ppm choline-chloride was added. NOEL = 300 (Clinical symptoms were observed for CCC at 1000 ppm and for CC (1000 ppm) + choline-chloride (700 ppm). The symptoms were more apparent at 1000 ppm (CCC only). Excessive salivation and weakness of the hind quarters were observed 2-3 hours after feeding and again after a further 6-7 hours. The death of 1 male and 1 female (found in the front of their kennels) occurred at 22 and 36 days, respectively. It is thought, the inability of these two dogs to jump into their kennels (weakness of hind quarters) to avoid exposure to the cold (frost on the ground) led to their deaths. The CC (1000 ppm) + CC (700 ppm) group also salivated slightly more than normal; however, symptoms slowly disappeared with time, particularly after re-scheduling the daily feeding ration to two times instead of one time/day. Overall body weight gain (male: 2.3 kg versus 1.8 & 1.5 kg) and food consumption (350 g versus. 330 & 322 g) means indicated a slight decrease at 1000 ppm CCC, compared to control.) UNACCEPTABLE. Not upgradeable (Major deficiencies too numerous to list). (Kishiyama & Silva, 12/9/02)

ONCOGENICITY, RAT

50508 - 002 037683 "Bioassay of 2-Chloroethyl) Trimethylammonium Chloride (CCC) for Possible Carcinogenicity," (B. Ulland; NCI Frederick Cancer Research Center, Frederick, MD; Technical Report Series #: 158, 1979). CCC technical (purity = 97-98% stated, 90% analyzed) was fed in diet to F344 rats (50/sex/dose treated, 20/sex/dose control) at 0, 1500 or 3,000 ppm for 108 weeks. NOEL > 3000 ppm (There were no treatment-related effects in either sex.) No adverse effects indicated. UNACCEPTABLE. Not upgradeable (inadequate number of control animals; too few CCC dose levels, numerous major deficiencies). (Kishiyama & Silva, 12/10/02)

ONCOGENICITY, MOUSE

50508 - 002 037684 "Bioassay of (2-Chloroethyl) Trimethylammonium Chloride (CCC) for Possible Carcinogenicity", (B. Ulland, NCI Frederick Cancer Research Center, Frederick, MD;Technical Report Series No.158, 1979). CCC technical (purity = 97-98% stated, 90% = analytical results) was fed in diet to B6C3F1 mice (20/sex/dose, control; 50/sex/dose treated) at 0, 500 or 2,000 ppm for 102 weeks. Body weight slightly lower for low and high dose females. NOEL = 500 ppm (Statistically significant increase in hepatocellular carcinomas in males at 2000 ppm.) **Possible adverse effect indicated: increase in the incidence of hepatocellular carcinomas in males** (7/20 in controls and 23/49 at 2000 ppm; not significant in pair-wise comparison but significant by Cochran-Armitage trend test)**.** UNACCEPTABLE. Not upgradeable (inadequate number of control animals; too few CCC dose levels). (Kishiyama & Silva, 12/10/02).

50508 - 002 037681 "Long-Term Feeding Study of Cycocel in the Mouse," (Wheldon, G.H.; Hunter, B., Hague, P., Spicer, E.J.F., Huntingdon Research Centre, Huntingdon, England; 5/5/71). Cycocel technical (purity = 98.5%) was fed in diet to Swiss mice (52/sex/dose) at 0 (untreated) and 1000 ppm for 78 weeks. NOEL = 1000 ppm (Body weight was slightly reduced 2 - 6% and 2 - 7% for males and females, respectively at 1000 ppm. This effect, however was not statistically significant.) No adverse effect indicated. Not acceptable and not upgradeable (too many major deficiencies). (Kishiyama & Silva, 12/6/02)

REPRODUCTION, RAT

50508 - 003 037685 "Chronic Reproductive Study in Three Generation of Wistar-Rats", (Leuschner, F., Leuschner, A., Schwerdlfeger, W.; Laboratory of Pharmacology and Toxicology, BASF; 4/14/67). CCC (purity not stated) was fed in diet to Wistar rats (20/sex/dose/generation) at 0, 100, 300 or 900 ppm (8.4 - 13.4, 24.3 - 39.9 and 71.1 - 118.8 mg/kg, respectively) throughout P, F1 and F2 generations (2 litters/generation) and to 9 weeks of age for the 2nd F2 litter (F3b). Parental NOEL > 900 ppm (There were no treatment-related effects on any parental generation.) Reproductive NOEL > 900 ppm (There were no treatment-related effects on reproduction.) Pup NOEL = 300 ppm (The report considered testicular giant cells to represent development at the stage of spermatogenesis. The relationship of giant cells to treatment was reported as unlikely but not impossible.) Not acceptable and not upgradeable. It is not possible to determine the possiblility of adverse effects based on the lack of data. Kishiyama & Silva, 11/25/02

50508 - 003 037686 "Trial of the Long-term Tolerance of a Mixture of Chloro-Choline Chloride (CCC) and Choline Chloride (CC) - Abbreviated to "CCC + CC" - in a Reproduction Experiment over Three Generations on Sprague-Dawley Rats", (Leuschner, F., Hübscher, F., Dontenwill, W.; Laboratory of Pharmacology and Toxicology, BASF; 4/17/75). The test article: 59% Chloro-choline chloride (CCC) and 41% choline chloride (CC) was fed in diet to Sprague-Dawley rats (20/sex/dose) at 0, 170, 510, 1530 or 4590 ppm (equivalent to: 12.5 - 18.8 mg/kg; 38.8 - 58.7 mg/kg; 115.8 - 178.0 mg/kg; 340.4 - 515.7 mg/kg, respectively) for 3 generations (2 litters/generation) through age 9 weeks of F3 pups. Reproduction, Systemic and Pup NOEL > 4590 ppm (There were no treatment-related effects at any dose.) Supplemental study (Rationale for dose selection not given; test article formulation contains two active ingredients). (Kishiyama & Silva, 11/26/02)

TERATOLOGY, RAT

** 50508 - 009 117572 "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Definitive Study with AC 38,555 in Rats", (E.A. Lochry, Argus Research Laboratories, Inc., Horsham, PA, Lab. Project ID #: 101- 011, 12/5/90). AC 38,555 (66.1% pure) was administered by gavage to mated Sprague-Dawley Crl: CD® BR VAF/PLUS® female rats (25/dose) at 0, 30, 90 or 180 mg/ml during gestation days (GD) 6-15. Maternal NOEL = 30 mg/kg/day (Body weight and food consumption

were decreased at ≥ 90 mg/kg. There was an increase in clinical effects (excess salivation, chromorhinorrhea, decreased motor activity, tremors, ataxia, lacrimation and rales) at 180 mg/kg.) Developmental NOEL >180 mg/kg/day (There were no treatment-related effects at any dose.) No adverse effect. Acceptable. (Kishiyama & Silva, 12/20/02).

50508 - 004 037688 "Teratological Evaluation of Cycocel in Rats", (Bailey, D.E., Morgareidge, K., Food and Drug Research Laboratories, Lab. No. 2288, 3/6/75). Cycocel (98% pure) was administered by gavage to mated FDRL-Wistar derived stock rats (30/dose) at 0, 25, 50 or 125 mg/kg during gestation days 6-15. The initial high dose of 250 mg/kg was removed after 1 week of dosing due maternal toxicity and a dose of 25 mg/kg was added. Maternal NOEL > 125 mg/kg (There were no treatment-related effects at any dose) Developmental NOEL >125 mg/kg (There were no treatment-related effects at any dose) This study is not acceptable and not upgradeable (deficiencies too numerous). No adverse effect indicated. (Kishiyama & Silva, 12/18/02).

50508 - 001 031819 Summary of 037688, above.

50508 - 004 037687 "Study of the Effect of Dietary Administration of CCC + CC (mixture of 59% Chlorocholine Chloride and 41% Choline Chloride) on the Prenatal, Perinatal and Postnatal Development of Rats", (F. Leuschner, Laboratory of Pharmacology and Toxicology, BASF, 5/28/75). Chlorocholine Chloride (59%) plus Choline Chloride (41%) were fed in diet to mated Sprague-Dawley rats (30/dose control; 40/dose treated) at 0 (diet), 300, 900 and 2700 mg/kg (20 control terminated the day before delivery, 10 control terminated lactation day 21; 20/dose treated GD 0 - 19, then terminated just prior to delivery; 10/dose treated GD 0 through Lac Day 21; 10/dose treated GD 0 - 19, then pups were delivered and observed 3 weeks *post-partum.*) **Maternal NOEL =** 900 mg/kg/day (Body weights were decreased and animals showed clinical signs (piloerection, slight ataxia, exophthalmos, cachexia) at 2700 mg/kg.) **Developmental NOEL =** 900 mg/kg/day (Increased resorptions and fetal deaths and decreased crown-rump length and fetal body weights occurred at 2700 mg/kg.) No adverse effect indicated. The effects to fetuses and pups were associated with maternal toxicity. Supplemental study. (Kishiyama & Silva, 12/17/02).

TERATOLOGY, RABBIT

** 50508 - 010 117574, "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Definitive Study with AC 38,555 in Rabbits," (Hoberman, A.M., Argus Research Laboratories, Inc., Laboratory Project ID #: ARGUS 101- 010; 10/23/90). Chlormequat chloride (AC 38,555, 66.1% pure) was administered by gavage to artificially inseminated New Zealand white rabbits (20/dose) at 0, 5, 20 or 35 mg/kg/day during gestation Days 7-19. Maternal NOEL = 5 mg/k/day (Mortality was increased at ≥ 20 mg/kg (statistically significant at 35 mg/kg.) A statistically significant body weight decrease occurred on gd 7 - 8 and gd 7 - 17 at 35 mg/kg. Food consumption was decreased at 35 mg/kg.) Developmental NOEL > 35 mg/kg/day (There were no treatment-related developmental effects.) ACCEPTABLE with no adverse effects. (M. Silva, 11/22/02)

50508 - 007 069785 "Study of the Prenatal Toxicity of 2-Chloroethyltrimethylammonium Chloride (Chlormequat Chloride) on Rabbits" (Hofmann, H.Th., Merkle, J.; BASF Gewerbehygiene und Toxikologie, Switzerland, 3/16/79). Chlormequat chloride (purity = 99%) was administered by gavage to artificially inseminated Himalayan ChBB:HM rabbits (14 - 21/dose) at 0,1.5, 3.0, 6.0 or 12.0 mg/kg during gestation days (GD) 6-18. **Estimated Maternal NOEL** = 6.0 mg/kg (There was a reduction in body weight gain at ≥ 12.0 mg/kg gestation days 6 - 12.) **Developmental NOEL** >12 mg/kg (There were no treatment-related developmental effects at any dose.) No adverse effect indicated. Not acceptable and but possibly upgradeable upon submission of requested information: There was no analysis of dosing material to confirm content, homogeneity and stability. The test article was not fully described. An explanation is required for the mention on page 19 of a dead control animal, when this death was not reported in the tabulated data. No summary tables or individual data for clinical

observations (diarrhoea, salivation, respiration, apathy, etc.); no justification for using x-ray for skeletal analyses and no individual data for food consumption were included in the report. (Kishiyama & Silva 12/24/02)

GENE MUTATION

** 50508 - 008 116038 "Evaluation of CL 38,555 in Mammalian Cell CHO/HGPRT Mutagenicity Test," (K.A. Traul, Genetic Toxicology Laboratory, American Cyanamid Co., Princeton, NJ; Lab Project ID #: 90-05-001, 11/20/90). CL 38,555 (purity = 66.1%, aqueous solutions) was assayed with CHO/HGPRT cells at 500, 1250, 2500, 3500, 4500 and 5000 ug/ml (with + without S9 metabolic activation) in two mutagenicity trials. Mutation frequency was statistically significantly increased at 2500 ug/ml inTrial 2 but it was not dose-related nor was it observed in Trial 1. Therefore, CL 38555 at doses up to 5000 ug/ml was not considered to be mutagenic. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 12/2/02).

** 50508 - 008 116039 "Evaluation of CL 38,555 in a Microbial/Microsome Mutagenicity Test" (K.A. Traul, American Cyanamid Co., Agricultural Research Division, Princeton, NJ; Lab Report No. 92-02-001, 10/24/90). CL 38,555 (purity = 66.1%, aqueous solution) was assayed with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Escherichia coli* strain WP-2 uvrA- at 0, 100, 500, 1000, 2500, and 5000 ug/plate (+/-S-9 metabolic activation) for 48 hours to test for mutagenic potential. Two trials were performed and a third partial trial was also performed to retest spurious results in the previous trials. A positive response was observed in each trial at a single dose; however, the responses were not dose-related, nor were they repeatable. CL 38555 up to 5000 ug/plate was not genotoxic. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 12/3/02)

50508 - 005 037689 "Report on the Testing of Reg. No. 24 605 in the Ames Test", (H. Zeller and G. Englehardt, BASF Gewerbehygiene and Toxikologie, 8/15/79). Chlormequat Chloride (92.4% pure) was tested with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at 0 (distilled water), 4, 20, 100, 500 or 2500 ug/plate (4 cultures/strain/dose, with & without S-9 metabolic activation) for mutagenic potential for 48 hours. There was no increase in reverse mutations after treatment with Chlormequat chloride (either with or without S9). Positive controls functioned as expected. UNACCEPTABLE (highest concentration used was not justified and no cytotoxicity was evident from the data as reported.) Upgrade is questionable. No adverse effect indicated. (Kishiyama & Silva, 12/11/02)

CHROMOSOME EFFECTS

** 50508 - 008 116040, "Evaluation of Cycocel® (CL 38,555) in the *In Vivo* Chromosome Aberration Assay in Rat Bone Marrow Cells," (R.K. Sharma, American Cyanamid Co., Princeton, NJ; Genetic Toxicology Laboratory Lab Report No: 90-14-001, 1/14/91). Cycocel® (66.1% pure, aqueous solution) was administered in a single gavage dose to Sprague-Dawley rats (5/sex/dose/harvest time) at 0 (sterile Mill-Q water), 125, 250 or 500 mg/kg with harvest times of 12, 24 or 48 hours. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 12/4/02).

50508 - 005 037692, "Study of Possible Mutagenicity of 59% Chlorocholine Chloride (CCC) and 41% Choline Chloride (CC) - Shortly "CCC +CC" - on the Bone marrow Cells of Treated Chinese Hamsters," (F. Leuschner, Laboratory of Pharmacology and Toxicology, Hamburg, Germany, 6/19/75). CCC (59%) + CC (41%), was administered as a single oral dose to female Chinese hamsters (6/dose) at 0 (distilled water), 200, 600 or 1800 mg/kg. Chromosomes were examined for aberrations at 6, 24 and 48 hours after treatment. NOEL > 1800 mg/kg (There were no treatment-related effects at any dose.) No adverse effect indicated. Not acceptable. (Justification for use of 2 chemicals, excluding males, dosing material not analyzed and Trenimon dose not provided.) (Kishiyama & Silva, 12/13/02).

DNA DAMAGE

50508 - 008 116041 "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocytes Cultures by Autoradiography with AC 38,555," (K.J. Pant, Sitek Research Laboratories, Rockville, MD; Lab. Report No: 0150-5100, 11/12/90). AC 38,555 (66.1% pure, aqueous solution) was assayed with Sprague-Dawley rat primary hepatocyte cultures at 0 (culture media), 0 (water), 0 (ETOH), 2.5, 4.0, 5.0 and 7.5 ul/ml to test for genotoxicity. AC 38,555 did not induce unscheduled DNA synthesis in cultured rat hepatocytes. The positive controls functioned as expected. No individual data were included in the report. No adverse effect. UNACCEPTABLE (see page 4 for requested data) (Kishiyama & Silva, 12/4/02)

50508 - 005 037690 "Study of 2-chloroethyltrimethylammonium Chloride (= chlorocholine chloride) in the Dominant Lethal Test on Male Mice after a Single Oral Administration," (Zeller, H., Englehardt, G., BASF Gewerbehygiene and Toxikologie, Switzerland, 5/25/79). Chlormequat chloride technical (99.6% pure) was administered once orally to NMRI mice (40 males/dose) at 0 (distilled water) or 261 mg/kg. Treated males were mated with untreated females (1:1). The same males cohabited 4 days with new females in each of 12 breeding periods. The significant increase in dominant lethal mutation in the second mating period was reported as a toxic rather than a mutagenic effect. Clinical signs were also observed (irregular respiration, a crouching position and piloerection) that were reversed by 2 - 3 hours. There were no positive control and only a single dose level was used without justification. Unacceptable but possibly upgradeable. No adverse effect. (Kishiyama & Silva, 12/11/02.

50508 - 005 037691 "Study of the Mutagenic effect (Dominant Lethal Factors) of Chlorocholine Chloride (CCC) and Choline Chloride (CC) - Briefly "CCC +CC" - on the Male Mouse Following Administration", (F. Leuschner, Laboratory of Pharmacology and Toxicology, BASF, Hamburg, Germany, 5/30/75). CCC (59%) + CC (41%), administered by gavage to NMRI mice (60/dose) at 0 (distilled water), 200, 600, or 1800 mg/kg/day for 5 days. Treated males were mated with untreated females (1:3) for 8 matings (each mating was for 7 days with new females). Systemic NOEL = 600 mg/kg/day (There was an increased incidence in mortality at 1800 mg/kg. Clinical signs of sedation were observed after treatment at 1800 mg/kg.). Dominant Lethal NOEL > 1800 mg/kg (There were no treatment-related effects at any dose.) A positive control was not included. The test compounds exceeded the MTD. No adverse mutagenic, dominant lethal effect indicated. Supplemental study. (Kishiyama & Silva, 12/13/02).

NEUROTOXICITY

Not required at this time.